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EFFICACY OF NAVIGATED SUBTHRESHOLD YELLOW MICROPULSE LASER FOR THE TREATMENT OF DIABETIC MACULAR EDEMA

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Introduction

Diabetic retinopathy (DR) is a leading cause of vision loss among adults, affecting millions of people worldwide.[1] The main cause behind vision impairment in DR is diabetic macular edema (DME), which is characterized by the accumulation of fluid and inflammatory factors in the retina.[1,2] DME can be divided into two categories: center-involving DME (CI-DME) and non-center-involving DME (nCI-DME), depending on whether the macula is affected.[2-19]

Traditional laser therapy was the primary approach for DME treatment, but the introduction of anti-VEGF treatments has changed the landscape.[20-25]

Traditional laser therapy had significant drawbacks, including damage to the retina and various complications.[11,12]

The subthreshold micropulse laser (SMPL) has emerged as an alternative to traditional laser therapy, as it avoids the retinal damage associated with conventional laser treatments.[26,27]

SMPL uses short bursts of laser energy with specific duty cycles to minimize heat effects.[26,27]

It appears to induce a biological response in the damaged retinal pigmented epithelium (RPE) and has been associated with reduced VEGF levels and improved macular capillary permeability.[26-28]

However, there is currently no standard protocol for SMPL treatment, leading to variations in laser power, duty cycle, and pulse duration.[26,27]

The introduction of the Navilas system (Navilas®, OD-OS GmBH, Teltwo, Germany) allows for the integration of various imaging modalities, such as fluorescein angiography, indocyanine green angiography, and spectral domain-optical coherence tomography (SD-OCT), to identify visible leakage points and area of retinal edema. These images are used to plan laser treatment.

The aim of this study is to evaluate the safety and effectiveness of subthreshold micropulse laser in treating non-center-involving DME over a 6-month follow-up period.

This treatment was administered using a navigated laser system that utilizes OCT maps to precisely delineate the treatment area.

Additionally, the study involves a comparison between two groups of patients: one group received treatment with fixed laser parameters, while the other have personalized laser parameters determined through titration testing. Both groups underwent treatment with subthreshold yellow micropulse laser at a 5% duty cycle for DME.

This research aims to provide valuable insights into optimizing navigated subthreshold micropulse laser as a treatment for DME.

Diabetic retinopathy

Epidemiology, risk factors and phatogenesis

DR is a microvascular complication of diabetes mellitus (DM), representing the leading cause of preventable blindness among individuals in the working-age range in numerous countries.[1,2]

In the United States, approximately 40% of individuals with type 2 diabetes and 86% of those with type 1 diabetes are affected by diabetic retinopathy.[2,3]

This high prevalence is mirrored in several other nations and on a global scale, this prevalence rate is estimated to be 34.6%, encompassing approximately 93 million people.[3]

There is some evidence suggesting a potential decrease in the prevalence of diabetic retinopathy, especially among individuals with type 1 diabetes, in the USA and other developed countries. This decrease could be attributed to better management of systemic risk factors in diabetes care.[2,3]

The primary risk factors are associated with the duration of diabetes, elevated blood glucose levels, and changes in metabolic pathways. These factors collectively trigger oxidative stress and initiate neurodegeneration during the early stages of diabetic retinopathy.[3]

Several biochemical mechanisms have been proposed to influence the development of retinopathy by affecting cellular metabolism, signaling pathways, and growth factors. These pathways include the buildup of sorbitol and advanced glycation end-products (AGEs), oxidative stress, activation of protein kinase C, inflammation, and the upregulation of the renin-angiotensin system and vascular endothelial growth factor (VEGF), among others.[4]

Recognition of the potential roles for these processes has led to development of new therapeutic agents, several of which have been or are being tested in clinical trials.[4]

Moreover, recent evidence indicates that inflammation assumes a significant role in the development of DR.[4,5] When exposed to hyperglycemia and other stressors like dyslipidemia, a variety of inflammatory mediators become overexpressed in individuals with diabetes.

This, initiates parainflammatory responses that have the potential to disrupt normal interactions between white blood cells and the endothelial lining, ultimately leading to damage in the microvasculature of the retina and to the vascular endothelium.[4,5]

Consequently, this disruption of the blood-retinal barrier leads to the development of microaneurysms and small intraretinal hemorrhages.[4] Subsequently, the leakage of various inflammatory cytokines and plasma proteins results in the observation of hard exudates during fundoscopic examination. All these clinical signs could be observed in the early stages of the non-proliferative diabetic retinopathy (NPDR). As the disease advances, vasoconstriction and the obstruction of capillaries give rise to tortuous capillaries and retinal ischemia. This stage may also present with the presence of 'cotton wool spots.'[4]

In the advanced stages of diabetic retinopathy, severe oxygen deficiency triggers the formation of new blood vessels (neovascularization), which can lead to vitreous hemorrhage and detachment of the retina, typical features of the proliferative diabetic retinopathy stages (PDR).[4]

Diabetic macular edema

Definition and epidemiology

DME is characterized by the thickening of the central part of the macula in the retina and represents the predominant cause of vision loss in individuals with diabetes mellitus.[6]

In fact, the vision deterioration linked to diabetic retinopathy primarily results from DME, affecting approximately 20% of individuals with diabetic retinopathy.[2]

The occurrence of macular edema is not exclusive to individuals with diabetes but is a frequent reaction to various retinal issues. The tendency for edema to affect the macular region likely arises from the macula's heightened vulnerability to both ischemic and oxidative stress, as well as its distinctive anatomical characteristics, such as loose intercellular adhesion and the absence of Müller cells in the fovea.[7]

Substantial variations in the prevalence and frequency of DME have been documented across various epidemiological investigations.[6,8,9]

These variations are contingent on factors such as the diabetes type (type I or II), the method of treatment (insulin, oral hypoglycemic agents, or dietary management alone), and the average duration of diabetes. [6,8,9]

DME can manifest at any stage of diabetic retinopathy (DR), but its likelihood increases as the duration of diabetes and the severity of DR progress. [6,8,9]

In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the ten-year incidence of DME was 20.1% among individuals with type I diabetes, 13.9% among individuals with type II diabetes who were not using insulin, and 25.4% among those with type II diabetes who were using insulin.[10]

The prevalence of DME escalates with the severity of DR: it affects 3% of eyes with mild nonproliferative diabetic retinopathy (NPDR), rises to 38% of eyes with moderate to severe NPDR, and reaches a prevalence of 71% in eyes afflicted with proliferative diabetic retinopathy (PDR). [6,8-10]

Classification

The diagnosis of macular edema is primarily clinical. Traditionally, stereoscopic fundus photography has been considered the gold standard for diagnosing diabetic DME.[6]

While fluorescein angiography is not a mandatory diagnostic tool for DME, it offers valuable insights. It provides a qualitative assessment of vascular leakage, aids in identifying treatable lesions, and is crucial for evaluating the enlargement of the foveal avascular zone (FAZ), which may indicate a poor visual prognosis.[6]

Conventionally, DME is defined as either retinal thickening or the presence of hard exudates within one disk diameter of the macular center. The term 'clinically significant macular edema' (CSME) was introduced to categorize disease severity and establish a threshold for laser photocoagulation.[11]

Besides this ophthalmoscopic classification, DME can also be categorized into focal and diffuse forms.[6]

Focal macular edema is characterized by localized areas of retinal thickening, typically resulting from focal leakage originating from individual microaneurysms or clusters of microaneurysms. Fluorescein angiography clearly reveals microaneurysms as the primary source of dye leakage, often delineated by a partial or complete ring of hard exudates with a circinate appearance.[6]

Diffuse macular edema, on the other hand, is linked to extensive damage to capillaries, microaneurysms, and arterioles, resulting in more widespread thickening of the macula due to generalized abnormal permeability of the retinal capillary bed. Diffuse macular edema tends to be symmetrical and lacks significant exudation.[6]

Cystoid macular edema, often associated with diffuse macular edema, occurs due to the breakdown of the blood-retinal barrier, leading to fluid accumulation in a petaloid pattern, primarily in the outer plexiform and inner nuclear layers.[6]

Regarding the pathogenesis, DME can be classified into prevalently retinovascular or nonretinovascular types. Prevalently retinovascular DME is characterized by abnormal permeability of retinal capillaries and is primarily caused by retinal vascular changes, including pericyte loss,

microaneurysm formation, and inner blood-retinal barrier breakdown. Fluorescein angiography is essential for distinguishing between these two types.[6]

DME can also be influenced or exacerbated by factors like persistent vitreomacular traction, macular traction due to tractional proliferative membranes, and a thickened and taut posterior hyaloid.[12]

These factors can exert tangential macular traction and contribute to edema.[12]

In summary, diagnosing DME involves various clinical and imaging techniques, and the classification of DME types can be complex due to overlapping features. Understanding the underlying pathogenic mechanisms can aid in determining the most appropriate treatment approach.[6]

The role of OCT

Optical coherence tomography (OCT) is a noninvasive, noncontact instrument, which provides cross-sectional, high-resolution images of the retina and a quantitative assessment of retinal thickness with a high degree of accuracy and reproducibility.[6]

The advantage of OCT in diagnosing CSME as compared to fundus biomicroscopy is its ability to provide an objective, quantitative, measure of retinal thickness as well as additional morphological details.[13]

Correlation between OCT and fluorescein angiography findings in the course of CSME is fairly good: about 60% of patients with foveal thickening and homogeneous intraretinal optical reflectivity on OCT have focal leakage on fluorescein angiography, while more than 90% of patients with diffuse cystoid leakage exhibit foveal thickening with decreased optical reflectivity in the outer retinal layers or foveal thickening with subretinal fluid accumulation on OCT.[14]

Furthermore, OCT clearly visualizes the vitreoretinal interface and reveals the presence and extent of vitreomacular traction and epiretinal membrane.[13]

More recently, a new OCT-based diagnostic tool has been developed; OCT angiography is a new noninvasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow data, producing angiographic images.[15]

An international clinical disease severity scale has been developed for DR and DME.[16] This scale, based on the ETDRS classification of DR and on the data collected in clinical trials and epidemiologic studies of DR, was proposed with the aim to improve communication between ophthalmologists and primary care physicians involved in diabetic patient care. According to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales, eyes with apparent DME are separated from those with no apparent thickening or lipid in the macula (DME present and absent); an additional division is based on the distance of retinal thickening and/or lipid from the fovea.[6, 16]

The term Clinically Significant Macular Edema (CSMO) was coined during the ETDRS study, which investigated laser photocoagulation as a treatment for diabetic macular edema (DMO).[11]

CSMO was defined based on slit lamp examination as follows:

- Retinal thickening occurring within 500 μm of the center of the macula.
- Presence of hard exudates within 500 μm of the center of the macula when associated with thickening of the nearby retina.
- Retinal thickening exceeding the size of >1-disc area, with any part of it located within 1-disc diameter (DD) of the center of the macula.[6,11]

This classification is applicable and useful for laser treatment of DME.[11]

The introduction of OCT has brought about a substantial enhancement in the morphological assessment of the macular region, thereby advancing our comprehension of diabetic macular edema (DME).[6]

This updated classification system distinguishes between two distinct entities: center-involving diabetic macular edema (CI-DME) and non-center-involving diabetic macular edema (nCI-DME).[6,12,17]

The key criterion for differentiation is whether the edema affects the fovea or central subfield. [6,12,17]

Pathogenesis of Diabetic Macular Edema

In both DR and DME, there is an imbalance between proangiogenic and antiangiogenic factors, with a predominant elevation in VEGF.[6]

High levels of VEGF lead to increased expression of the inflammatory intercellular adhesion molecule-1 (ICAM-1), resulting in retinal capillary leukostasis, a crucial factor in diabetic microangiopathy.[4-7]

The high VEGF expression in the vitreous of DR and DME patients is mainly due to hypoxia, triggered by the obstruction and loss of retinal capillaries.[4-7]

Indeed, VEGF, which is elevated in the vitreous of DR patients, plays a pivotal role in vascular changes, blood-retinal barrier (BRB) disruption, and the induction of angiogenesis.

Macular edema can manifest as either cytotoxic or vasogenic.[4-7]

Cytotoxic edema occurs initially and is associated with increased levels of substances like sorbitol, lactate, and phosphates in the intracellular space due to hyperglycemia. Vasogenic edema, on the other hand, can be induced by various molecules, including VEGF, nitrous oxide, and free radicals, causing a breach of the inner BRB.[4-7]

The presence of both cytotoxic and vasogenic lesions in diabetic patients leads to reduced pericytes, Müller cells, and astrocytes, coupled with an increase in basal membrane capillaries and a decrease in endothelial cells, ultimately resulting in hyperpermeable retinal vessels due to inner BRB rupture.[4-7]

Müller cells, the primary glial cells in the retina, play a crucial role in maintaining interstitial liquid homeostasis. However, in diabetes, Müller cell metabolism is disrupted, leading to dysfunction in liquid transport and subsequent cellular swelling, extracellular fluid accumulation, and cyst formation.[18]

DR and DME are now recognized as concurrent vascular and neuronal degenerative processes. Emerging evidence suggests that neuronal impairment may precede the appearance of vascular lesions in DR.[6]

In normal conditions, there's a close interaction between the cellular and vascular components of the retina to maintain necessary homeostasis for normal functioning.[18]

Microglial cells, along with Müller cells and astrocytes, appear to initiate retinal inflammation, with reactive glial cells amplifying this response.[118] This low-grade inflammation is sustained by the production of cytokines like interleukin 6 (IL-6), interleukin 8 (IL-8), and C-C motif ligand 2. These cytokines have consistently shown elevated levels in DR and DME patients, positively correlating with disease severity.[18] They alter the function of astrocytes, affect the integrity of the retinal capillaries, and impact the retina's ability to manage glutamate.[18] Additionally, IL-8 and CCL2 attract white blood cells, contributing to perivascular infiltration in affected retinal areas.[18]

Morphological OCT Biomarkers of Diabetic Macular Edema

The advent of spectral domain OCT (SD-OCT) and swept-source OCT (SS-OCT) has significantly enhanced the study of macular structure. These technologies have expanded the assessment of various morphological biomarkers in diabetic macular edema (DME), which play a prognostic role in treatment.[19]

Currently, OCT is an invaluable and indispensable tool in patients with diabetes to determine the need for treatment and prognosticate patients with DME.[13,19]

Intraretina Cystoid Spaces: The size and location of intraretinal cystoid spaces are significant factors influencing the functional outcomes of individuals with diabetic macular edema (DME).[19] In DME, elevated VEGF levels disrupt the inner blood-retinal barrier, resulting in increased vascular permeability, reduced osmotic gradient, extracellular fluid accumulation, and the formation of cysts.[13,19]

Unlike cysts in cystoid macular edema (CME), cystoid spaces in DME can lead to photoreceptor damage and impact visual outcomes.

Intraretinal cystoid spaces in the macula can be classified based on their size, which can be categorized as small (< 200μm) or large (≥ 200μm). The presence of large cysts is linked to a poorer visual prognosis, and the size of these cysts is associated with the extent of macular ischemia.[19]

As the severity of macular ischemia increases, both the horizontal and vertical diameter of the cysts tend to increase.

When analyzing cystoid macular edema (CME), several other parameters should be considered, including the cyst's location relative to the center of the macula, its lateral extension, the extent of anatomical damage to the inner and outer retinal layers caused by the cystoid changes, any accompanying damage to photoreceptors or the retinal pigment epithelium (RPE), and the presence of associated subretinal fluid (SRF). These characteristics can have an impact on the baseline visual acuity and how patients respond to treatment.[13]

Subfoveal serous retinal detachment: The prevalence of subfoveal serous retinal detachment in individuals with diabetic macular edema (DME) ranges from 15% to 30%[19]. Serum albumin has been identified as a sensitive marker for detecting the presence of SRF. Hypoalbuminemia can reduce intravascular osmotic pressure, contributing to fluid retention in the subretinal space due to increased hydrostatic pressure.[19]

The role of SRF in determining final visual and anatomical outcomes in DME remains somewhat unclear. Some studies have suggested that the presence of SRF is associated with favorable anatomical and functional improvements, while others have linked it to poor visual gains.[13]

Research, such as the RESTORE study and post hoc analysis from the RISE/RIDE study, has indicated a protective role of SRF, showing better visual gains in eyes with baseline SRF after treatment with ranibizumab therapy.[19]

Similarly, studies evaluating the effect of vitrectomy in diffuse DME have reported better visual gains in eyes with SRF. Post hoc analyses of VIVID-DME and VISTA-DME studies have shown that intravitreal aflibercept yielded superior visual outcomes compared to laser therapy, regardless of baseline SRF status, although a greater treatment effect was observed in patients with baseline SRF.[19]

Research by Moon and colleagues has indicated that DME eyes with SRF tend to respond significantly to dexamethasone implants, supporting their use in such cases. Eyes with SRF have also shown increased interleukin-6 (IL-6) levels, suggesting active inflammation.[19]

Some studies have demonstrated a better response to dexamethasone implants in the presence of SRF.[13]

In summary, our understanding of the relationship between SRF status and visual outcomes in DME is still evolving and requires further investigation through long-term studies.

Disorganization of retinal inner layers (DRIL): refers to the inability to differentiate between specific layers within the retina, including the ganglion cell layer–inner plexiform layer complex, inner nuclear layer, and outer plexiform layer.[19]

DRIL can occur with or without center-involving diabetic macular edema (DME). It is assessed using OCT B-scans within the central 1 mm retinal zone, and when more than 50% or >500μm of this area is disorganized, it is considered significant.[19]

This disorganization is linked to a poorer visual prognosis in eyes with edema or resolved edema, making DRIL a reliable biomarker for predicting visual acuity in DME.[20]

The inner retinal layers affected by DRIL include axons, bipolar cells, and amacrine cell nuclei, all crucial for visual signal transmission from photoreceptors to the ganglion cell layer.

DRIL signifies damage to these structures, leading to abnormal visual processing. Studies have shown that early changes in DRIL can predict visual outcomes during treatment, with an increase in DRIL over a 4-month period predicting a decline in visual acuity.[20]

Furthermore, DRIL has been correlated with macular capillary non-perfusion and the size of the foveal avascular zone (FAZ).

Recent research has also linked DRIL to the severity of DR, particularly proliferative DR (PDR). The presence of DRIL is associated with disruption in the outer retinal layers, specifically the ellipsoid zone (EZ) and external limiting membrane (ELM).[19] In summary, DRIL serves as a valuable OCT biomarker for assessing visual acuity, capillary perfusion, and other morphological changes in DME.

Hyperreflective retinal foci (HRF) are observed as intraretinal hyperreflective dots in OCT scans of individuals with retinal conditions like diabetic macular edema (DME).[13,19]

These HRF represent subclinical lipoproteins that leak into the retina following the breakdown of the inner blood-retinal barrier.[19]

Subretinal HRF are linked to the presence of subfoveal hard exudates once subretinal serous detachment resolves. Some researchers propose that HRF may represent activated microglial cells, as they found increased soluble CD14 in the aqueous humor, a substance released by activated microglial cells. Initially present in the inner retinal layers, HRF later migrate to the outer retinal layers. Key characteristics of HRF include their size (less than 30μm), lack of back-shadowing, and reflectivity similar to the retinal nerve fiber layer. HRF serve as important imaging indicators of retinal inflammation.[19]

Studies have shown that the size and number of HRF may decrease following treatment with anti-VEGF drugs and corticosteroid implants.[20]

In fact, recent research suggests that corticosteroid implants may yield better outcomes than anti-VEGF agents in DME patients with HRF, especially when a larger number of HRF is initially present.[19,20]

There is ongoing exploration into how HRF relate to visual acuity, and it has been suggested that a higher number of HRF on OCT may be associated with early DME recurrence after steroid implant therapy.[20]

Therefore, patients with an elevated number of HRF on OCT scans should be closely monitored for potential early intervention if necessary.

Integrity of the Ellipsoid Zone: the condition of the outer retinal layers serves as a direct indicator of the well-being of the retinal photoreceptors and RPE.[20] Research has indicated that eyes with an intact inner segment/outer segment (IS/OS) junction tend to experience more significant visual improvements following treatment.[19]

The status of the IS/OS junction can be categorized as fully continuous, partially disrupted, or entirely disrupted. Individuals with long-standing DME may exhibit localized or diffuse loss of the external limiting membrane (ELM) and ellipsoid zone (EZ).[19]

Studies have demonstrated that patients with disruption in the outer retinal layers tend to achieve suboptimal gains in visual acuity.[19,20]

Visual acuity has been found to positively correlate with the preservation of the ELM and EZ, emphasizing their importance in visual outcomes.[19]

Epiretinal surface: In patients with diabetic retinopathy (DR), there are abnormalities in the vitreous known as diabetic vitreopathy. These vitreous changes lead to an unusual type of posterior vitreous detachment (PVD) characterized by strong adhesions between the vitreous and the retina, resulting in incomplete detachment.[19]

Additionally, the posterior hyaloid can form a sheet along the posterior pole, causing tractional forces and mechanical distortion of the retina. This condition is referred to as a taut posterior hyaloid membrane (TPHM) and is responsible for stubborn cases of macular edema. Patients with TPHM can benefit from a surgical procedure called pars plana vitrectomy, which involves removing the taut hyaloid.[19]

OCT Angiography Biomarkers of Diabetic Macular Edema

Optical Coherence Tomography Angiography is an innovative and valuable tool for assessing the microvasculature of the retina and choroid.[15]

It provides detailed information that complements what is obtained through Fluorescein Angiography (FFA).[15]

OCTA offers advantages such as the ability to precisely identify areas of capillary nonperfusion, detect collateral vessels, assess neovascularization in the retina or optic nerve head, and identify abnormalities in the foveal avascular zone (FAZ).[15]

What sets OCTA apart is its capacity to separately analyze each of the three retinal capillary plexi, which is crucial for understanding the pathophysiological changes in DR.[15]

Unlike FFA, which produces dynamic images, OCTA generates static images of retinal blood flow. OCTA has the ability to detect various abnormalities, including microaneurysms, intraretinal microvascular abnormalities (IRMAs), areas of capillary non-perfusion, and neovascularization, even before these changes become clinically apparent or are visible on fundus photography.[15]

In some cases, OCTA can identify microaneurysms that may not be detected using FFA.[15]

Vessel density (VD) is a measure of the proportion of blood vessel area within a defined region compared to the total area measured.[21]

In patients with diabetic retinopathy (DR), VD decreases in both the superficial capillary plexus (SCP) and deep capillary plexus (DCP).[21]

Notably, VD reductions have also been observed in diabetic patients who do not have DR, suggesting that these changes may be early indicators of diabetic vascular pathology.[15,21]

Additionally, it has been found that parafoveal capillary non-perfusion in the DCP can serve as an early sign of DR.[15]

After the administration of dexamethasone, VD remains largely unchanged in both the SCP and DCP. However, there is a tendency for VD to increase in the choriocapillaris following treatment.

Foveal Avascular Zone: OCTA allows for quantitative measurements of the foveal avascular zone (FAZ) using various indices, including axis ratio, FAZ area, acircularity index, perimeter, and area.[15]

In patients with diabetes, larger FAZ measurements, including acircularity index and axis, have been observed in the deep plexus slab on OCTA scans, regardless of the presence of diabetic retinopathy (DR).[15,21]

Furthermore, eyes with DRIL exhibit significantly larger FAZ compared to eyes without DRIL.[19]

Treatment of Diabetic Macular Edema

The treatment background for DME has evolved significantly in recent years, primarily influenced by NICE and SMC guidelines.[12]

Managing systemic factors like blood pressure and blood sugar control is crucial for individuals with diabetes, particularly when dealing with macular edema. Effective control of blood pressure can significantly reduce edema.[12]

Current treatment options for DME include initial intravitreal therapies using anti-VEGF drugs, followed by potential laser therapy or the administration of steroids like dexamethasone or fluocinolone implants.[12,13]

Anti-VEGF therapies are favored due to their ability to target VEGF-A, a critical cytokine responsible for retinal vascular leakage.[13]

Intravitreal steroid use is supported by evidence indicating the role of inflammation in DME development, involving factors like leukostasis, upregulation of inflammatory mediators such as ICAM-1 and IL-6, along with increased VEGF-A levels.[13]

DME without central involvement

For DME without central involvement, the ETDRS study found that laser treatment reduced the risk of moderate visual loss by 50% compared to observation. However, it rarely led to vision improvement.[11]

The exact mechanism of macular laser treatment is not fully understood but may involve cytokine release from retinal pigment epithelium or Müller cells.[12]

Since the ETDRS study, various retinal laser systems and wavelengths, such as argon green, yellow, or diode, have been developed for DME treatment.[12]

Subthreshold grid laser therapy has also emerged to reduce the side effects of conventional macular laser treatment, with some studies showing similar efficacy; however, subthreshold laser therapy is not widely used in the for DME treatment.[12]

The treatment approach for DME without central involvement depends on the location of microvascular changes.[12] If these changes are far from the fovea and associated with significant fluid/exudate, laser therapy may be considered. However, waiting for fluid to involve the fovea before intervention is also a reasonable option, which many ophthalmologists worldwide recommend.[12]

Central involvement DME

For Central involvement DME, treatment decisions are influenced by visual acuity, central subfield thickness observed through OCT examination, and patient preferences.[12]

According to NICE guidance:

1. Ranibizumab: It is recommended as an option for treating visual impairment caused by DME if the eye has a central retinal thickness of 400 μm or more at the start of treatment.[12] The RESTORE study showed significant visual acuity improvement in ranibizumab-treated groups compared to laser monotherapy.[22]
2. Aflibercept: Recommended for eyes with visual impairment due to DME with a CRT greater than 400 μm at the beginning of treatment. The VIVID and VISTA studies demonstrated substantial visual acuity gains with aflibercept injections.[23]
3. Fluocinolone acetonide (Iluvien): Recommended for treating chronic DME that doesn't respond well to other therapies, especially in pseudophakic eyes. The recommendation is

based on the FAME Study, where a significant percentage of patients experienced notable visual improvements with fluocinolone acetonide treatment.[24]

4. Dexamethasone implant (Ozurdex): Suggested as an option for treating chronic DME that is insufficiently responsive to available therapies in pseudophakic eyes, based on results from the MEAD study. Ozurdex retreatment every 6 months showed improved visual outcomes compared to sham treatment.[25]

These guidelines provide valuable options for managing CI-DME based on CRT and clinical trials' outcomes, allowing ophthalmologists to tailor treatment choices to individual patient needs.[12]

Laser treatment for Diabetic Macular Edema

In the treatment of DME, macular laser therapy remains effective and necessary, even in the era of anti-VEGF therapies.[12]

It is considered the treatment of choice for cases of none-center-involved CSME to prevent future vision loss, as per the ETDRS.[11,12]

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends intravitreal anti-VEGF agents for more severe forms of center-involved DME with a central retinal thickness (CRT) on OCT of 400 μm or more. However, for milder forms of DME (CRT < 400 μm), macular laser treatment is preferred and advised because it is clinically effective and more cost-effective than anti-VEGF agents.[12]

NICE's decision is based on evidence that showed when CRT was less than 300 μm, there was no significant difference in treatment efficacy between anti-VEGF agents and laser therapy, but laser therapy was more cost-effective. Even in cases with CRT between 300 and 400 μm, the vision gains with anti-VEGF agents were only slightly better than those with macular laser therapy, and the clinical relevance of this difference was uncertain.[12] Additionally, a significant percentage of patients receiving anti-VEGF agents still required macular laser therapy to control DME.[12]

Macular laser treatment can be performed using continuous wave lasers, resulting in a visible burn in the retina, known as threshold laser therapy (standard laser therapy or SL therapy). While the exact mechanism of action is not fully understood, it is believed to act on viable retinal pigment epithelium (RPE) cells around the treatment area. However, there is a possibility of damage to adjacent retinal layers, including photoreceptors, due to heat conduction during the procedure. However, this treatment had significant drawbacks, including the destruction of photoreceptors, choroidal neovascularization, proliferation of retinal Müller glia, and the formation of epiretinal membranes.[12]

Complications of conventional laser photocoagulation included central scotomas (blind spots in the central vision), deterioration of color and night vision, decreased contrast sensitivity, accidental foveal burns, and enlargement of laser scars. The procedure was also associated with pain and could lead to increased intraocular pressure.[12]

Subthreshold Micropulse Laser for Diabetic Macular Edema

Subthreshold micropulse laser (SMPL) is a novel retinal laser technique that is considered safer for retinal tissue compared to conventional continuous wavelength lasers.[26]

Unlike conventional lasers, SMPL does not induce protein coagulation, preventing the formation of retinal scars and tissue damage.[26,27]

It has been found effective in treating DME, leading to improvements or stabilization of visual function and a reduction in macular thickness.[27] However, the exact mechanism of how SMPL works is still being studied.[26]

One proposed mechanism is that SMPL targets the retinal pigment epithelium (RPE), which releases heat shock proteins (Hsps), particularly Hsp 70, in response to the treatment.[28]

This stress-induced response leads to immunomodulation of retinal cells, activation of repair processes, and a decrease in the production of inflammatory cytokines, VEGF, and matrix metalloproteinases.[28]

SMPL has also been reported to reduce the concentration of inflammatory cytokines in the aqueous humor secreted by retinal glial cells, including Müller cells and microglial cells, in eyes with DME.[29] This suggests that SMPL may help downregulate the inflammatory processes triggered by hyperglycemia in diabetes mellitus.[29]

SMPL is a safe and non-damaging therapeutic approach that differs from classic retinal photocoagulation.[27-29] It specifically targets the RPE, minimizing the formation of chorioretinal scarring. [28]

SMPL has a slower onset of effects, typically noticeable around the third month after treatment, but it offers a longer-lasting impact on the retina.[27]

SMPL uses short repetitive laser impulses, allowing the treated tissue to cool down between impulses to prevent thermal burns.[28] The treatment involves setting a duty cycle (DC) of 5% to 15%, where each impulse lasts 100–300 μs and is followed by a 1700–1900 μs interval without energy transmission.[26]

There are no fixed parameters for SMPL, and different settings for spot diameter, pulse duration, power, and the number of delivered spots have been proposed.[26]

Laser power can be fixed or adjusted based on the non-edematous area of the peripheral retina. The laser spots should be applied without spacing over the entire macular area between the vascular arcades, covering both the edematous retina and the foveal center.[26]

One challenge of SMPL is that the laser spots are not visible, making it difficult to confirm the procedure's accuracy. To address this, multi-spot systems are used to deliver spots in a regular pattern, such as a 7 × 7 matrix. This approach reduces treatment time, simplifies application, and enhances reliability.[26]

Purpose of the study

The aim of this study is to assess the safety and efficacy of subthreshold micropulse laser for the treatment of non-center-involving diabetic macular edema, in a 6 months follow period.

This treatment will be administered using a navigated laser system programmed with OCT maps to precisely define the treatment area.

Furthermore, the study will include a comparison between two groups of patients: one group receiving treatment with fixed laser parameters and the other with personalized laser parameters. The objective is to determine which treatment option is more effective.

Methods

In this prospective study were included 38 eyes of 38 diabetic patients diagnosed with treatment-naïve non-center-involving DME, treated with subthreshold micropulse laser.

All enrolled patients were treated and evaluated at the Retinal Center of the Ophthalmology Clinic of the University of Messina, Italy.

Prior to their participation, all patients provided informed consent after receiving a detailed explanation regarding the nature of the study and the potential consequences of the laser treatment. The Institutional Review Board of the University of Messina approved this study, ensuring adherence to the principles outlined in the Declaration of Helsinki.

The inclusion criteria consisted of patients aged >18 years old and DME with central macular thickness (CMT) < 400 micrometers, patients with best corrected visual acuity (BCVA) ≥ 78 letters Early Treatment Diabetic Retinopathy Study (ETDRS) score.

Exclusion criteria encompassed the following: any retinal condition other than diabetic retinopathy (DR); proliferative DR; a history of prior retinal surgery or laser treatment; cataract surgery performed within the last 6 months and the presence of any cataract that did not significantly impair visual acuity (initial lens opacity); glaucoma or a history of high intraocular pressure; any systemic neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, or Parkinson's disease;

uncontrolled systemic blood pressure, defined as values equal to or greater than 120/80; significant media opacity that hindered the acquisition of high-quality fundus images.

Anamnestic data were recorded for each patient, including the type and duration of diabetes and the recent glycated hemoglobin (HbA1c) levels.

A comprehensive ophthalmologic assessment was conducted, which comprised best-corrected visual acuity (BCVA) measurement using the ETDRS chart, microscopic evaluation of the anterior segment, applanation tonometry, and swept-source OCT imaging using the DRI SS-OCT Triton system (Topcon, Japan).

Data were collected at every patient visit laser treatment and after 6 months.

Optical coherence tomography analysis. SS-OCT images were taken using a 3D macula 7x7mm OCT scan centered on the fovea. The structural retinal biomarkers, including the presence of serous retinal detachment (SRD), central macular thickness (CMT), intra-retinal fluid (IRF), vitreo-macular adhesion (VMA), disruption of the integrity of the ellipsoid zone (EZ), disorganization of retinal inner layers (DRILs), and hyperreflective dots (HRD), were evaluated through automatic analysis using the OCT software IMAGEnet 6 (version 1.17.9720; Topcon Medical Systems Inc., Oakland, NJ, USA).

OCTA parameters: SS-OCTA imaging were taken using a 6x6 mm scan centered on the fovea. The instrument used for OCT-A image acquisition was the DRI OCT Triton plus which is based on the OCT-A Ratio Analysis (OCTARA) system to obtain motion contrast images.[30]

OCT-A scans obtained within a 6x6 mm area centered on the fovea were acquired for quantitative evaluation by an experienced technician, selecting only high-quality images for analysis.[30] The FAZ area was manually measured in square millimeters (mm^2), using the tool *caliper area* available within the software IMAGEnet 6 (version 1.17.9720; Topcon Medical Systems, Inc, Oakland, NJ, USA) at the level of SCP and DCP. The vessel density was measured in 6x6 mm OCT-A images using a software algorithm that automatically generated images of the SCP and DCP.[31,32]

Based on the default settings, the SCP's boundary was segmented from +2.6 μm of the inner limiting membrane (ILM) and +15.6 μm from the inner plexiform layer (IPL), while the DCP was segmented from +15.6 μm between IPL/ inner nuclear layer (INL) and +70.2 μm IPL/INL.[31]

The eye showing the better BCVA was chosen for analysis; in cases of equal BCVA the eye with higher VD was selected.

To assess the morphological macular changes in the SCP, the presence or absence of irregular FAZ area, capillary loss, capillary tortuosity, and crossing vessels were evaluated by two operators in a masked fashion (AM, OGW). Inter-observer accordance above 95% was achieved.

Subthreshold Micropulse Laser Treatment:

Treatment planning: a color and an infrared fundus photography of the retina and the macula area (Fig. 1), using a contactless lens.

The Navilas® 577 (OD-OS GmBH, Teltwo, Germany) software allow to introduce external images, and the OCT map with 9 Early Treatment Diabetic Retinopathy Study grid circles (Fig. 2) were introduced and are overlaid onto the Navilas® fundus image for indication-focused treatment planning (Fig. 3).

The images overlap was made considering four point of the arteriovenous crossings.

The plan is overlaid onto the live image, while Navilas® pre-positions the aiming beam on treatment locations (Fig. 3).

In group 1, the standard treatment parameters were, 100 μm spot size, 5% duty cycle, and 250 mW power, confluent spots, using a subthreshold 577-nm yellow light micropulse laser.[27]

In group 2, to define the appropriate power setting for micropulse laser treatment, we conducted a titration test in a non-edematous retinal area located outside the vascular arcade, utilizing a 100-μm spot size. Our typical approach began at 70mW, and we incrementally increased the power by 10–20mW until we achieved a burn that was just barely visible. At this point, we transitioned the laser to micropulse mode, multiplying the power used during the test burn by a factor of 4, while

maintaining a 200μm spot size. The number of contiguous laser spots employed varied depending on the extent of center-involving DME, with the treatment being applied above the regions of retinal thickening as observed in OCT. This "high-density" treatment was used to cover the area of increased macular thickness.

All laser procedures were consistently administered by the same ophthalmologist.

After laser treatment, patients received Bromfenac 0.9 mg/ml drops two times a day for ten days.

Statistical Analysis.

Statistical analysis entailed expressing numerical data as mean and standard deviation, while categorical variables were represented as absolute frequencies and percentages.

Normal distribution fitting was assessed using the Kolmogorov-Smirnov test.

To determine if there were statistically significant differences at different observation times, appropriate statistical tests were employed. For numerical variables, The Student's T-test for parametric data was applied to assess the significance of differences between baseline and treatment at baseline and 6-month data; Wilcoxon signed-rank test was used for non-parametric data, and the McNemar test for dichotomous variables.

Additionally, for each parameter, we performed statistical comparisons between groups using the Chi Square test for categorical variables and Mann Whitney test for numerical variables.

A significance level of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the prism graph pad software package for macOS.

Results

Demographic Information: Group 1 included a total of 19 patients, consisting of 6 females (31.6%) and 13 males (68.4%), all diagnosed with non-center-involving DME.

Among them, 12 patients had DME in their right eyes, and 7 patients had it in their left eyes.

Group 2 included 19 patients, 7 females (36.8%) and 12 males (63.2%), involving right eye in 10 patients, and left eyes in 9 patients.

All patients were of Caucasian ethnicity, with an average age at the time of DME diagnosis of 65.8 ± 12 years in group 1, and 66.4 ± 10.6 years in group 2.

In group 1, the mean duration of diabetes was 12 ± 7.3 years, and the mean HbA1c level was 8 ± 3.1%; whereas in group 2 the mean duration of diabetes was 13.1 ± 6.9 years, and the mean HbA1c level was 7.8 ± 4%.

Additionally, in group 1, 12 patients (46.15%) had arterial hypertension, and 11 patients (42.3%) had hypercholesterolemia, whereas in group 2, 11 patients (42.3%) had arterial hypertension, and 11 patients (42.3%) had hypercholesterolemia. No patients had kidney failure.

Four patients (15.3%) also had primary open-angle glaucoma, and 16 patients (61.5%) were phakic.

Visual Acuity: In group 1, at the baseline the mean BCVA was 84.6 ± 11.4 letters, whereas after 6 months, this changed to 84.3 ± 12.1 letters (p=0.82). In group 2, BCVA changed from 85.8 ± 12.1 letters to 85.6 ± 11.8 letters after 6 months (p=0.75). No statistically significant differences emerged comparing the two groups after treatment (p= 0.64).

OCT Parameters: At the baseline, in group 1, the mean CMT was 254.3 ± 32.6 μm, which changed to 258.7 ± 43.1 μm after 6 months (p=0.33) (Table 1).

In group 2, CMT changed from 256.2 ± 29.6 μm to 255.3 ± 35.1 (p=0.79) (Table 2).

Comparing the two groups, no statistically significant differences were observed after treatment (p=0.8) (Fig. 4).

In both groups, there were no significant changes in macular thickness in the 9 ETDRS sectors after 6 months (Table 1 and 2).

In group 1, one patient had SRD, ten patients had IRF, three patients had DRIL, and two patients had EZ disruption. After 2 months, IRF had completely resolved in 2 eyes (Table 1).

In group 2, 2 patients presented SRD, 10 had IRF, 2 DRIL, and 2 patients had EZ disruption. After 6 months, IRF was completely disappeared in 2 eyes (Table 2).

In both groups, no significant changes were observed in RNFL and paramacular GCL thickness after treatment (Table 1 and 2). Additionally, choroidal thickness did not show significant changes at the 6-month follow-up (Table 3).

In both groups, there were no cases of center-involving DME observed throughout the 2 months of follow-up.

OCTA Parameters: Initially, in group 1 the superficial FAZ measured 0.33 ± 0.17 mm2, which changed to 0.39 ± 0.2 mm2 after 2 months (p=0.07) (Table 4). There were no statistically significant changes in deep FAZ (p=0.06). Furthermore, foveal VD changed from 23 ± 4.3% to 22.8 ± 4.3% (p=0.28). No significant changes were observed for the 4 evaluated sectors (Table 4).

In group 2, the superficial FAZ was 0.33 ± 0.17 mm2 and after 6 months it changed to 0.39±0.2 mm2 (p=0.07), whereas the deep FAZ was 0.41 ± 0.27 mm2 and after treatment it changed to 0.43 ± 0.38 (p=0.06). No statistically significant changes were observed for foveal VD and in the other sectors (Table 4).

Additionally, comparing the two groups did not demonstrate statistically significant differences in the OCTA parameters after treatment (Fig. 5).

Safety parameters: No significant changes in mean IOP were observed throughout the follow-up period in both groups, going from 16.2 ± 2.4 mmHg to 16.8 ± 2.6 mmHg (p=0.39) in group 1, and from 15.7 ± 3.1 mmHg to 16.1 ± 2.9 mmHg (p=0.42) in group 2.

No adverse events were reported following treatments, and no chorio-retinal scars were observed at the end of the follow-up.

Additionally, there were no instances of intravitreal injections of anti-VEGF or dexamethasone intravitreal implant during the 6-month follow-up.

Discussion

According to the Early Treatment Diabetic Retinopathy Study, focal argon photocoagulation, which involves creating a visible burn, reduced the risk of moderate vision loss by 50% in cases of clinically significant DME.[11]

While this treatment proved effective, it had several drawbacks, including the destruction of photoreceptors, the development of choroidal neovascularization, and the secondary proliferation of retinal Müller glia, ultimately leading to the formation of epiretinal membranes.[11,12]

Complications associated with this treatment included central scotomas, deterioration of color and night vision, decreased contrast sensitivity, accidental burns in the foveal region, and enlargement of laser scars.[12]

Current indications for conventional laser treatment are limited to cases of vasogenic DME with focal capillary leakage, DMEs with a thickness below 300 μm, and instances of persistent vitreomacular adhesion. It is considered a secondary treatment option for resistant cases and non-fovea-involving edema.[12]

Subthreshold micropulse laser treatment is a novel technique that utilizes cell photostimulation to reduce the overall laser energy applied.[26,27]

Unlike traditional retinal photocoagulation, MPLT is a safe and non-damaging therapeutic approach, specifically targeting the RPE while minimizing chorioretinal scarring.[26,27]

This treatment has a slower onset of action, becoming noticeable around the third month after the procedure, but it provides longer-lasting effects on the retina.[27]

MPLT achieves its safety by employing a series of short repetitive laser impulses, allowing the treated tissue to cool down between pulses, thus avoiding thermal burns. [26,27]

A key parameter in MPLT is the duty cycle, typically set between 5% to 15%, which determines the effective duration of laser work. [26,27]

There are no standardized parameters for MPLT, and various settings for spot diameter, pulse duration, power, and the number of spots delivered have been proposed.[27-29]

Laser power can be fixed or adjusted based on the non-edematous area of the peripheral retina.[33]

The laser spots should be applied densely across the entire macular area between the vascular arcades, covering the edematous retina and the foveal center. [27-29]

A challenge in performing MPLT is that the laser spots are invisible, making it difficult to confirm the accuracy of the procedure. [27-29]

To address this, multi-spot systems are used to deliver spots in a regular pattern, which reduces treatment time, simplifies application, and enhances reliability. [27-29]

In our study, we conducted a comparison between two treatment approaches. The first one involved fixed parameters, which were determined based on previously published data, while the second utilized variable power settings based on a titration test.

After a 6-month evaluation, no discernible differences were observed in terms of efficacy and safety between these two MPLT treatment protocols. Consequently, utilizing a fixed treatment strategy in MPLT offers two significant advantages: it minimizes treatment duration and reduces the likelihood of errors that might occur during the transition from continuous to micropulse mode due to incorrect titration.

MPLT can be performed using lasers with various wavelengths, including 532 nm (green), 577 nm (yellow), 810 nm (infrared), or 670 nm (red). Different wavelengths target specific structures in the retina and have varying degrees of absorption by retinal components.

Currently, there is no consensus on the most favorable wavelength for MPLT in the treatment of DME and other macular disorders, but devices using these wavelengths have demonstrated a high safety profile and are recommended for MPLT. [27-29]

While specific indications for MPLT are not yet established, it is considered an alternative treatment for macular disorders such as DME, central serous chorioretinopathy, and macular edemas secondary to retinal vein occlusion. [27-29]

MPLT has been found to be efficient and devoid of adverse events in cases of mild to moderate macular edema with a CRT below 400 μm and relatively good visual acuity.[27]

In our study, there were no statistically significant changes in retinal thickness observed over the 6-month follow-up period. However, we did observe a noticeable reduction in IRF in 11 patients within the treated area, along with a decrease in hard exudates, demonstrating a remarkable effect on the edematous area treated.

An important finding was that none of the patients experienced an increase in retinal thickness in the central area or within the treated region, and none developed center-involving DME after 6 months. Furthermore, no significant changes in BCVA were observed throughout the follow-up period.

According with our findings, Nakamura et al. demonstrated that the functional improvement observed after MPLT was primarily limited to an increase in visual acuity.[34]

Their study found that macular sensitivity within the central 10 degrees, as assessed by microperimetry, did not show significant improvement despite improvements in BCVA and a reduction in foveal thickness.[34]

Furthermore, Luttrull et al. reported significant differences in CRT before and after MPLT, particularly in eyes with initial CRT measurements below 300 μm.[35]

The maximum reduction in CRT was observed between 4 and 7 months post-treatment, and BCVA remained stable, with significant improvement during the same period.[35]

Mansouri et al. noted that retinal thickness influenced the spread of laser energy and tissue response.[36] They compared the efficacy of MPLT based on the anatomical severity of edema and suggested MPLT as an effective and safe therapy for mild and moderate DME.[36]

However, eyes with initial CRT exceeding 400 μm did not respond to the treatment and required rescue anti-VEGF injections.[36]

The Central Retinal Thickness appears to be the primary prognostic factor for a positive functional response to MPLT in cases of DME; as a result, we specifically included patients with CMT measuring less than 400 micrometers.

Citirik et al. also found a correlation between the efficacy of micropulse laser and central retinal thickness.[37] Their study indicated that eyes that had previously received ineffective bevacizumab treatment responded well to MPLT if the CRT was not higher than 300 μm.[37]

Nicolò et al. suggested that MPLT may be less effective in eyes that had previously shown insufficient responses to focal or grid macular photocoagulation or anti-VEGF treatments.[38]

They reported a better response in treatment-naive patients, with stabilization or improvement in BCVA and CRT parameters.[38]

MPLT can also serve as an adjunct therapy alongside anti-VEGF agents, helping stabilize retinal parameters with fewer required injections.[27-29]

Valera-Cornejo et al. observed changes in BCVA only in previously untreated patients. It's important to note that in these studies, laser procedures were applied not only over the edematous areas but also across the entire macula, including the foveal center and unaffected retina.[39]

However, Abouhussein et al. arrived at a different conclusion, finding that a single session of MPLT was effective in patients with refractory DME measuring below 400 μm. Both of these studies had limitations, including short follow-up periods and small sample sizes without randomization.[40]

In terms of safety, we did not observe any retinal scars or damage to the RPE and EZ after the treatment. This finding is corroborated in numerous studies.[27-29]

Indeed, Kwon et al. found that MPLT did not lead to the formation of chorioretinal scars, even with repeated treatments and an increased number of micropulse shots.[41]

Their study showed similar efficacy between micropulse and conventional lasers.[41]

Inagaki et al. compared the efficacy of 810 nm and 577 nm MPLT in combination with focal microaneurysm photocoagulation.[42] Both wavelengths were effective in reducing CRT and

preserving visual acuity.[42] The 577 nm wavelength had the advantage of requiring less power and allowing for both micropulse and conventional therapies using the same device.[27-29]

Supplementary microaneurysm photocoagulation further reduced the recurrence rate. Marashi et al. supported the use of a hybrid threshold laser approach for microaneurysms alongside subthreshold micropulse high-density laser treatment, as it effectively stabilized DME with minimal scar formation.[43]

OCT-A is an innovative non-invasive diagnostic tool that allows for the visualization of vascular irregularities and microaneurysms in both the superficial and deep capillary networks.[21]

It also provides insights into changes such as the enlargement of the FAZ, non-perfused areas, and the presence of neovascularization.[21]

Vujosevic et al. have shed light on the mechanism of action of MPLT by demonstrating a reduction in inflammatory biomarkers detected using OCT and OCT-A.[27,29]

These studies observed a decreased number of hyper-reflective spots and microaneurysms, while the perfusion parameters in the chorioretinal vasculature remained stable in response to MPLT. Based on these results, our study did not reveal any statistically significant changes in either the deep or superficial FAZ. Additionally, there were no observed alterations in vessel density within the macular area.

The main limitations of this study include the small sample size in both of the enrolled groups and the relatively short follow-up duration, which may constrain the generalizability of these findings. Furthermore, gathering additional data related to ci-DME and including patients who have received prior laser treatment or anti-VEGF therapy could prove valuable in elucidating the prognostic factors in MPLT.

Conclusion

The introduction of SMPL represents a promising development in the treatment of non-center-involved diabetic macular edema and mild center-involved DME.

This approach helps mitigate the potential side effects associated with traditional laser photocoagulation in the macular region.

Our study confirmed the safety of this SMPL procedure by showing no discernible structural changes in the outer and inner retinal layers, choroidal structure, and retinal vascular plexi.

Consistent with prior research, we have observed significant positive outcomes in treatment-naïve DME patients with CMT measuring less than 400 microns.

Over a 6-month follow-up period, we noticed a reduction in intra-retinal fluid and hard exudates in the treated area for most patients who underwent SMPL.

Importantly, none of the patients experienced a worsening of DME, and there was no need for intravitreal anti-VEGF injections throughout the follow-up period.

The decision to use a 6-month follow-up aligns with earlier studies that have shown the maximum effect of SMPL typically occurring within 4-6 months. Furthermore, SMPL allows for retreatment in non-responders, and prior studies have considered the possibility of increasing the duty cycle from 5% to 10% in such cases.

Additionally, our study involved a comparison between two treatment approaches: one utilizing fixed parameters established based on previously published data, and the other using variable power settings based on a titration test. After evaluating the outcomes over a 6-month period, no significant differences were observed in terms of both efficacy and safety between these two SMPL treatment protocols. Consequently, adopting a fixed treatment strategy in SMPL offers two notable advantages: it reduces the treatment time and minimizes the potential for errors during the transition from continuous to micropulse mode, which can occur with incorrect titration.

Additionally, in our study, MPLT was administered using a navigated laser system (Navilas® 577) programmed with OCT maps to precisely delineate the treatment area. This approach also proved

valuable in reducing the invasiveness of the procedure, as it obviated the need for fluorescein angiography, which is commonly required to define the laser treatment area in cases of DME.

In conclusion, our findings have reaffirmed the efficacy and safety of SMPL when using a navigated laser system programmed with OCT maps over a 6-month follow-up. Moreover, adhering to a standardized and fixed treatment protocol has demonstrated positive outcomes in the treatment of non-center-involved DME.

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Tables

Table 1. Group 1: OCT biomarkers and macular thickness before and after treatment

Variables	**Baseline**	**6 months**	**p-value**
SRD presence, n (%)	1 (5.2)	1 (5.2)	0.99
IRF, presence, n (%)	10 (52.6)	8 (42.1)	0.42
DRIL presence, n (%)	3 (15.8)	2 (10.5)	0.63
EZ disruption, n (%)	2 (10.5)	2 (10.5)	0.99
IOP, mmHg	16.2 ± 2.4	16.8 ± 2.4	0.39
Macular Thickness, µm			
Center	254.3±32.6	258.7±43.1	0.33
Temporal inner	296.8±30.3	305.3±40.2	0.17
Nasal inner	303.5±21.6	304.2±23.5	0.76
Superior inner	302.2±26.3	301.2±25.2	0.75
Inferior inner	281.3±42.5	281±42.9	0.85
Temporal outer	260.8±38.5	264.9±30.2	0.33
Nasal outer	280.4±28.2	280.1±28.7	0.75
Superior outer	265.2±30.1	262.8±25.9	0.81
Inferior outer	255.1±25.7	257.2±28.6	0.80
RNFL Thickness, µm			
Center	10.8±9.6	10.3±10.2	0.7
Temporal inner	22±7.3	25.8±14.4	0.24
Nasal inner	28.4±7.2	28.9±8.5	0.44
Superior inner	34.2±9.3	35.1±12.9	0.49
Inferior inner	33.6±6.7	32.6±4.8	0.17
Temporal outer	22.4±8.2	24±7.2	0.42
Nasal outer	50.8±11.3	50.9±11.5	0.78
Superior outer	43.1±10.8	41.5±8.9	0.20
Inferior outer	42.1±10.5	42.3±11.2	0.63
GCL Thickness, µm			
Center	52.1±14.7	54.3±16.6	0.27
Temporal inner	81.8±12.5	82.6±16.7	0.68
Nasal inner	84.4±11.4	85.5±12.1	0.58
Superior inner	81.2±13.8	82.9±12.4	0.42
Inferior inner	80.5±14.7	84.2±14.2	0.13
Temporal outer	58.5±12.7	59.8±13.8	0.85
Nasal outer	66.4±13.1	68.9±16.2	0.35
Superior outer	58.5±12.7	59.8±13.8	0.57
Inferior outer	81.2±13.8	82.9±12.4	0.07

Legend: Legend: SRD - Serous retinal detachment; IRF- Intra Retinal Fluid; DRIL - Disorganization of the inner retinal layers; EZ – Ellipsoid zone; IOP- Intraocular pressure; RNFL- Retinal Nerve Fiber layer; GCL- Ganglion Cell Layer.

Bold characters for p-value < 0.05.

Table 2. Group 2: OCT biomarkers and macular thickness before and after treatment

Variables	**Baseline**	**6 months**	**p-value**
SRD presence, n (%)	2 (10.5)	2 (10.5)	0.99
IRF, presence, n (%)	10 (52.6)	8 (42.1)	0.42
DRIL presence, n (%)	2 (10.5)	2 (10.5)	0.99
EZ disruption, n (%)	2 (10.5)	2 (10.5)	0.99
IOP, mmHg	16.4 ± 2.1	16.5 ± 2.3	0.39
Macular Thickness, µm			
Center	256.2±29.6	255.3±35.1	0.79
Temporal inner	289.3±32.1	295.1±41.1	0.14
Nasal inner	301.2±22.1	302.1±24.1	0.69
Superior inner	300.6±23.1	301.9±23.2	0.55
Inferior inner	285.4±41.5	286±41.5	0.45
Temporal outer	263.1±32.5	2637±32.1	0.64
Nasal outer	283.1±24.2	281.1±25.3	0.25
Superior outer	256.6±32.2	265.2±24.2	0.14
Inferior outer	254.2±26.4	253.3±28.4	0.78
RNFL Thickness, µm			
Center	9.1±6.5	8.7±7.3	0.61
Temporal inner	21.6±6.7	21.3±7.4	0.19
Nasal inner	25.3±7.4	26.4±8.5	0.42
Superior inner	33.7±8.9	34.1±10.1	0.41
Inferior inner	33.5±6.3	34.1±5.3	0.21
Temporal outer	21.9±7.8	21.6±6.9	0.47
Nasal outer	51.5±12.1	52.1±11.59	0.69
Superior outer	41.1±11.2	41.1±8.5	0.24
Inferior outer	41.5±11.5	41.5±12	0.69
GCL Thickness, µm			
Center	52.9±14	54.9±14.1	0.39
Temporal inner	81.5±12.1	82±16.1	0.61
Nasal inner	83.1±12.1	83.1±12.8	0.44
Superior inner	82.1±11.7	82.1±13.1	0.69
Inferior inner	80.4±11.5	80.9±11.8	0.53
Temporal outer	54.1±12.1	54.5±12.1	0.75
Nasal outer	62.4±11.4	62.9±13.5	0.51
Superior outer	58.3±11.3	58.7±11.2	0.65
Inferior outer	81.5±13.1	82.1±13.4	0.21

Legend: Legend: SRD - Serous retinal detachment; IRF- Intra Retinal Fluid; DRIL - Disorganization of the inner retinal layers; EZ – Ellipsoid zone; IOP- Intraocular pressure; RNFL- Retinal Nerve Fiber layer; GCL- Ganglion Cell Layer.

Bold characters for p-value < 0.05.

Table 3. Choroidal Thickness

Group 1			
Variables	**Baseline**	**6 months**	**p-value**
Choroidal Thickness, μm			
Center	225±77.5	228.6±79.4	0.34
Temporal inner	213.2±70.7	217.1±70.4	0.12
Nasal inner	210.2±81.3	210.4±84.9	0.94
Superior inner	237.2±68.5	236.4±70.7	0.81
Inferior inner	166.1±74.1	167.2±76.6	0.68
Temporal outer	194.8±57.7	196.2±59.8	0.62
Nasal outer	167.9±80.9	168.3±83.7	0.84
Superior outer	224.6±68.1	225.4±67.9	0.67
Inferior outer	195.7±75.9	197.8±80.9	0.55
Group 2			
Variables	**Baseline**	**6 months**	**p-value**
Choroidal Thickness, μm			
Center	223.5±75	225.9±77.4	0.28
Temporal inner	214.1±72.3	215.2±71.2	0.23
Nasal inner	212.5±69.6	213.5±71.3	0.51
Superior inner	234.3±64.7	234.1±70.1	0.88
Inferior inner	169.2±77.2	168.7±76.5	0.68
Temporal outer	196.2±59.4	195.7±58.4	0.36
Nasal outer	167.9±80.9	166.8±89.2	0.34
Superior outer	227.9±69.4	228.1±71.2	0.57
Inferior outer	198.7±77.1	197.9±81.9	0.49

Bold characters for p-value < 0.05.

Table 4. OCTA parameters

Group 1			
Variables	**Baseline**	**6 months**	**p-value**
FAZ superficial, mm^2	0.33±0.17	0.39±0.2	0.07
FAZ deep, mm^2	0.41±0.27	0.43±0.38	0.06
VD, %			
Center	23±4.3	22.8±4.3	0.28
Temporal	40.6±3.6	41.7±2.9	0.12
Nasal	40.4±5.1	41.3±3.8	0.44
Superior	40.9±3.8	41.1±2.8	0.73
Inferior	40±4.6	40.1±3.9	0.89
Group 2			
Variables	**Baseline**	**6 months**	**p-value**
FAZ superficial, mm^2	0.33±0.12	0.36±0.2	0.42
FAZ deep, mm^2	0.39±0.14	0.40±0.38	0.4
VD, %			
Center	22.5±3.9	22.7±4.7	0.35
Temporal	41.2±3.8	41.6±2.5	0.20
Nasal	41.9±5.6	41.7±3.9	0.39
Superior	40.5±4.5	40.9±3.1	0.64
Inferior	41±4.4	41.3±3.8	0.76

Legend: FAZ- Foveal Avascular Zone; VD- Vessel Density.
Bold characters for p-value < 0.05.

Figure 1. Navilas fundus image of the macular area revealing the presence of microaneurysm and hard exudates

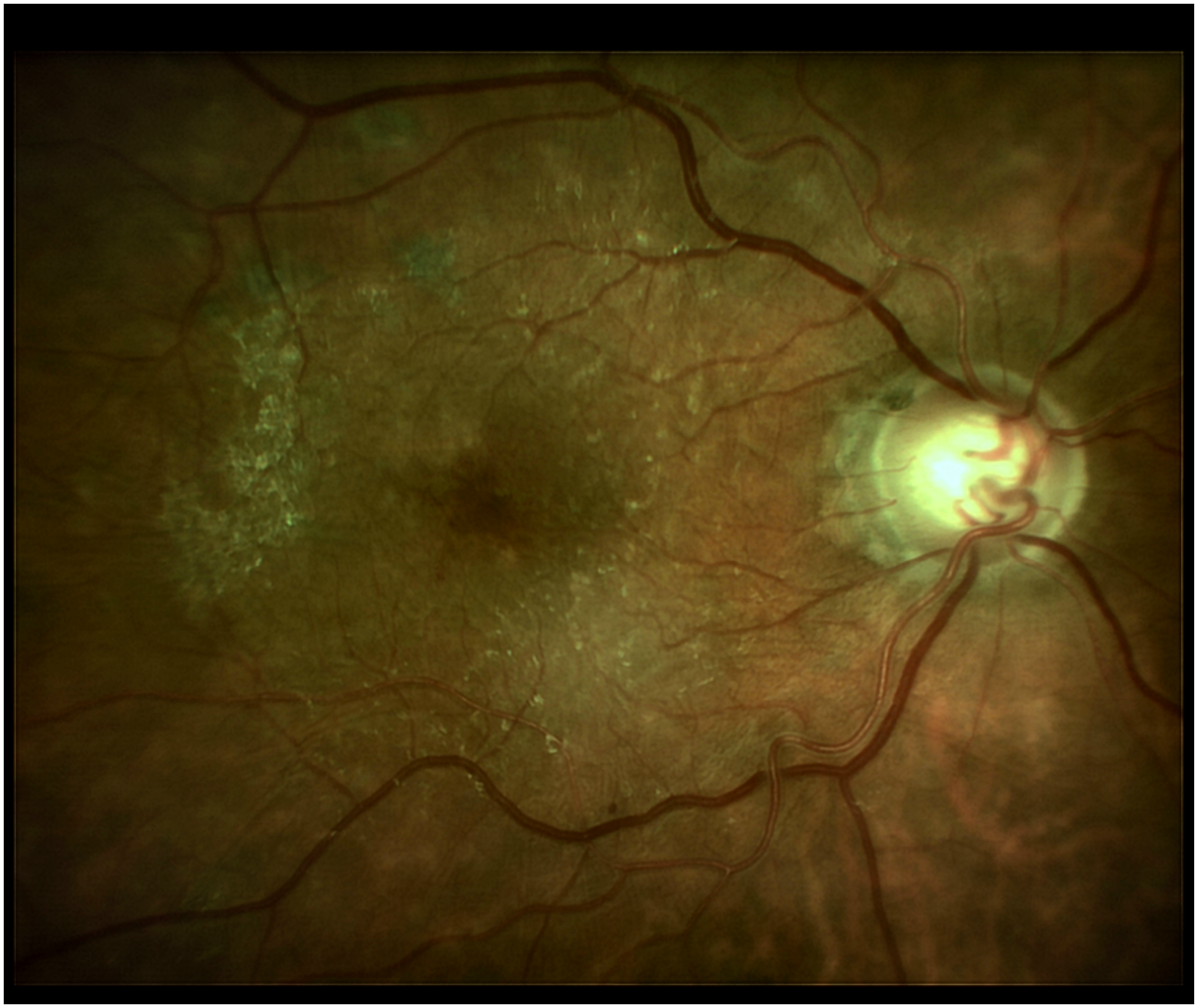

Figure 2. OCT thickness map with 9 ETDRS grid revealing an area of increased thickness

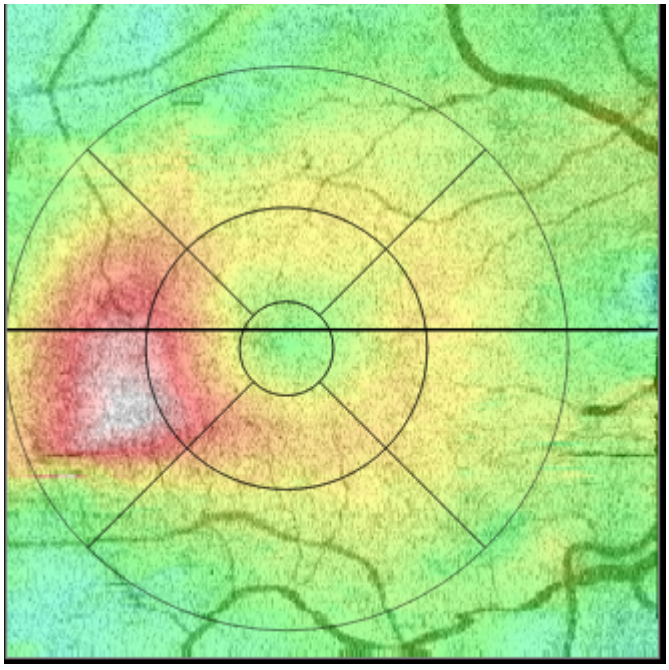

Figure 3.
A) An OCT thickness map featuring 9 ETDRS grid circles is superimposed onto the Navilas® fundus image. This overlay aids in planning treatment with a specific focus on the indicated areas.
B) The treatment plan encompasses the retinal region with heightened thickness as indicated by the OCT data, and two protection masks were positioned on the optic nerve and fovea region, respectively.

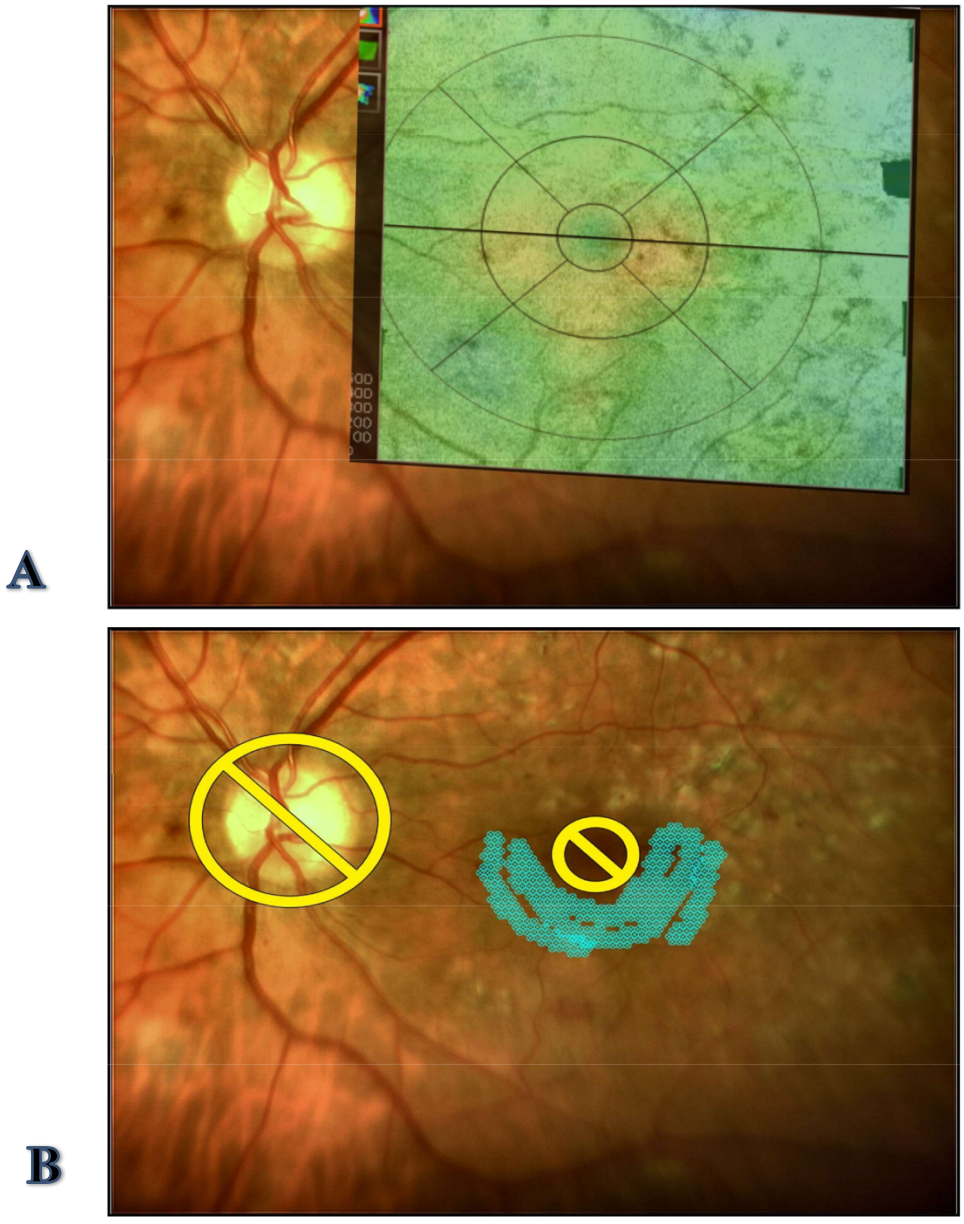

Figure 4. Box plots of central macular thickness (CMT), Retinal Nerve Fiber Layers (RNFL) thickness, and Ganglion Cell Layer (GCL) thickness.

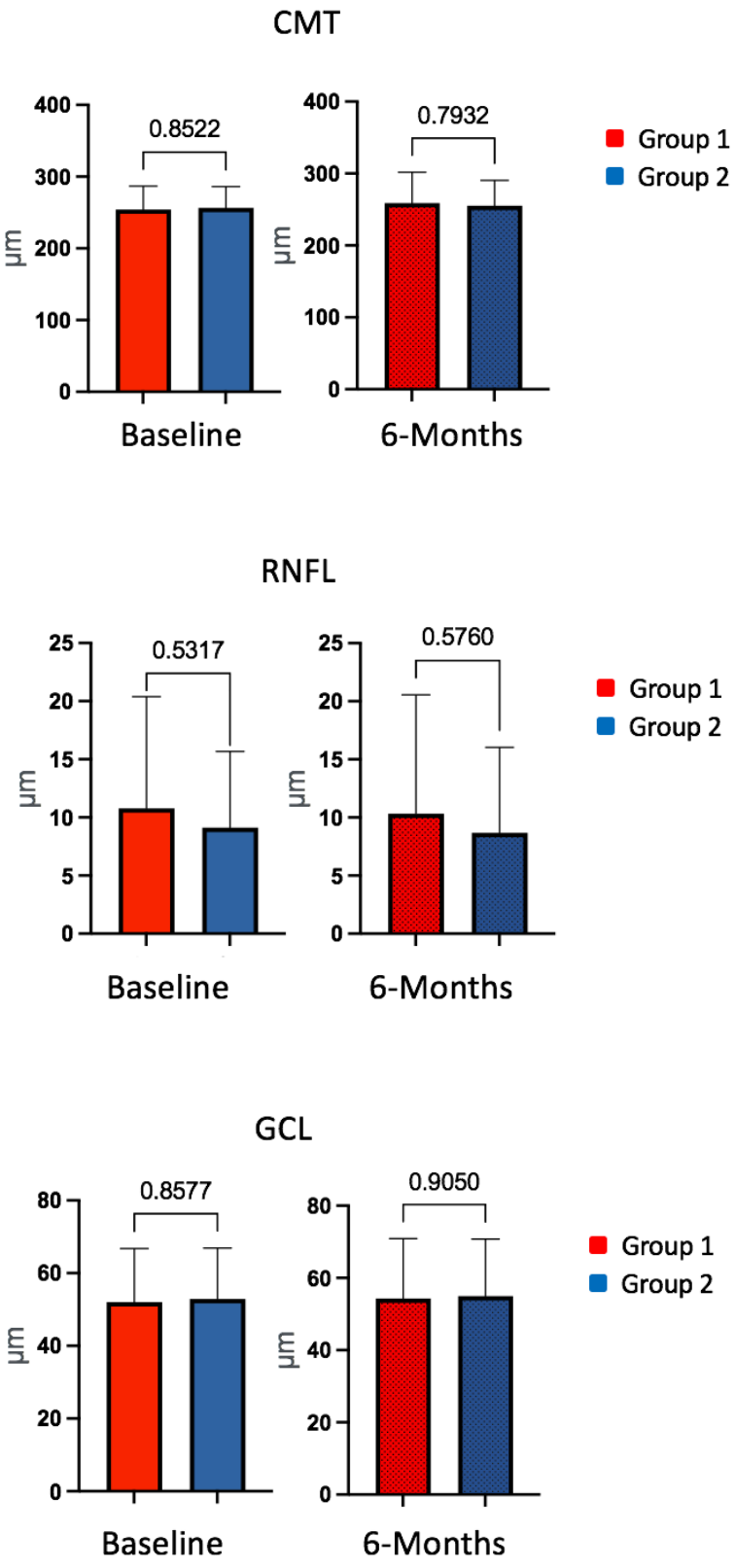

Figure 5. Box plots of OCTA data

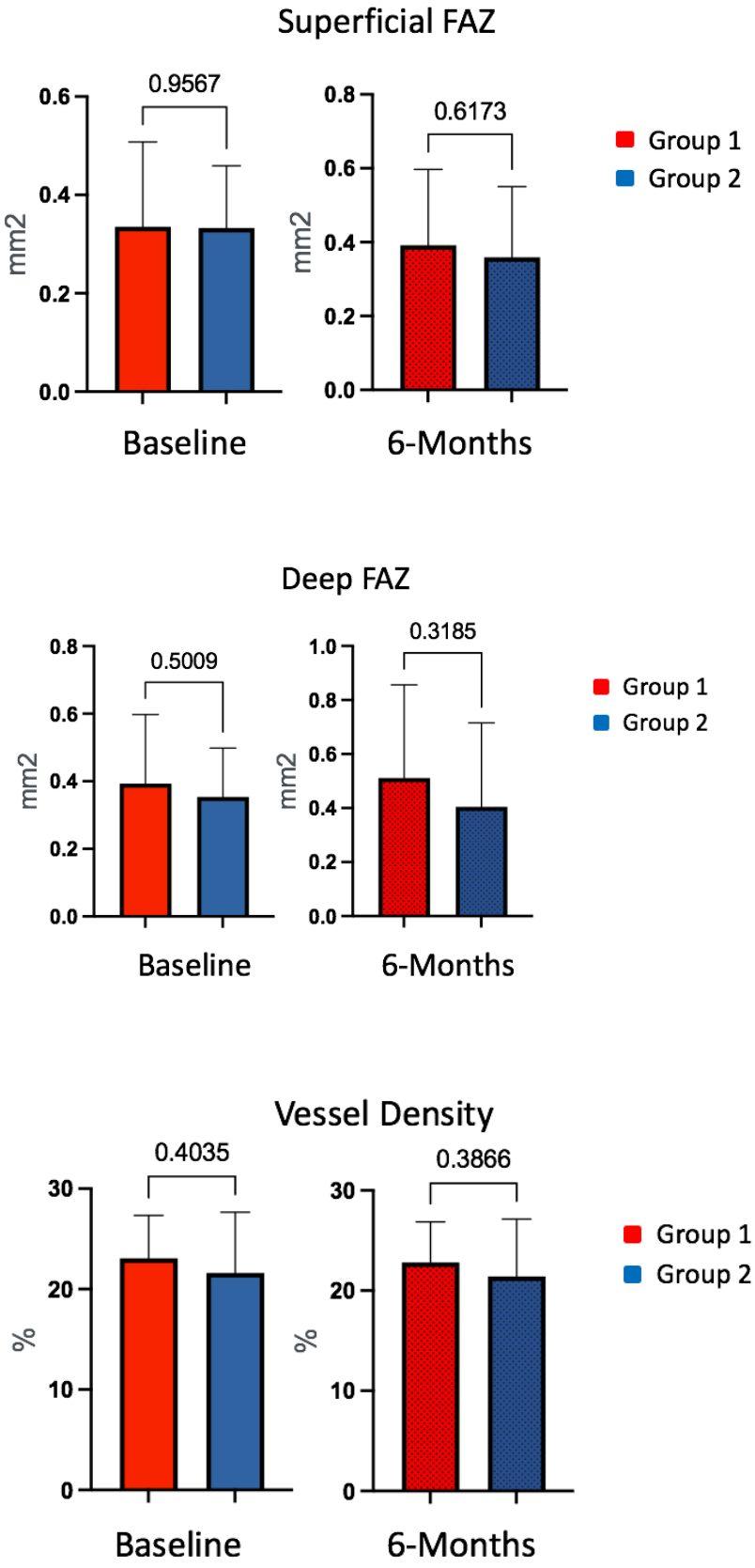

Figure 6. A case of a DME patient before and 6 months after treatment, illustrating a reduction in intra-retinal fluid."

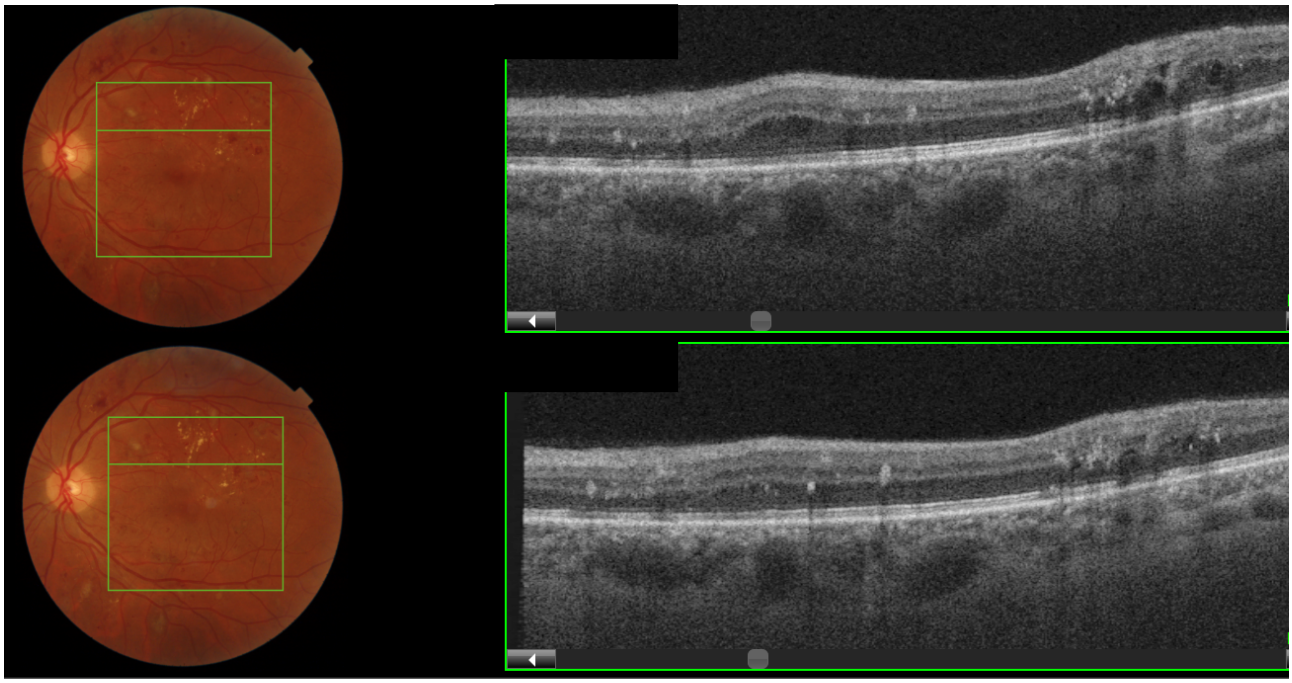

Figure 7. A case of a DME patient 6 months after treatment demonstrating a reduction in the volume of intra-retinal cysts."